

SPECIFICATION
(MBHB Case No. 99,423)

5 **TITLE: N-Pyrazole A_{2A} Receptor Agonists**

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20 **Application Type: Original Utility Patent Application**

Assignee: CV Therapeutics, Inc.

BACKGROUND OF THE INVENTION

Field of Invention

This invention includes N-pyrazole substituted 2-adenosine compositions that are useful
5 as A_{2A} receptor agonists. The compositions of this invention are vasodialating agents that are
useful as heart imaging aids that aid in the identification of mammals, and especially humans
who are suffering from coronary disorders such poor coronary perfusion which is indicative of
coronary artery disease (CAD). The compositions of this invention can also be used as
therapeutics for coronary artery disease as well as any other disorders mediated by the A_{2A}
10 receptor.

Description of the Art

Pharmacological stress is frequently induced with adenosine or dipyridamole in
patients with suspected CAD before imaging with T1 scintigraphy or echocardiography. Both
drugs effect dilation of the coronary resistance vessels by activation of cell surface A₂
15 receptors. Although pharmacological stress was originally introduced as a mean of provoking
coronary dilation in patients unable to exercise, several studies have shown that the prognostic
value of ²⁰¹Tl or echocardiographic imaging in patients subjected to pharmacological stress
with adenosine or dipyridamole was equivalent to patients subjected to traditional exercise
stress tests. However, there is a high incidence of drug-related adverse side effects during
20 pharmacological stress imaging with these drugs such as headache and nausea, that could be
improved with new therapeutic agents.

Adenosine A_{2B} and A₃ receptors are involved in a mast cell degranulation and,
therefore, asthmatics are not give the non-specific adenosine agonists to induce a
pharmacological stress test. Additionally, adenosine stimulation of the A₁ receptor in the
25 atrium and A-V node will diminish the S-H interval which can induce AV block (N.C. Gupta
et al.; *J. Am Coll. Cardiol*; (1992) 19: 248-257). Also, stimulation of the adenosine A₁

receptor by adenosine may be responsible for the nausea since the A_1 receptor is found in the intestinal tract (J. Nicholls et al.; *Eur. J. Pharm.*(1997) 338(2) 143-150).

Animal data suggests that specific adenosine A_{2A} subtype receptors on coronary resistance vessels mediate the coronary dilatory responses to adenosine, whereas subtype A_{2B} receptor stimulation relaxes peripheral vessels (note: the latter lowers systemic blood pressure). As a result there is a need for pharmaceutical compositions that are A_{2A} receptor agonists that have no pharmacological effect as a result of stimulating the A_1 receptor *in vivo*. Furthermore, there is a need for A_{2A} receptor agonists that have a short half-life, and that are well tolerated by patients undergoing pharmacological coronary stress evaluations.

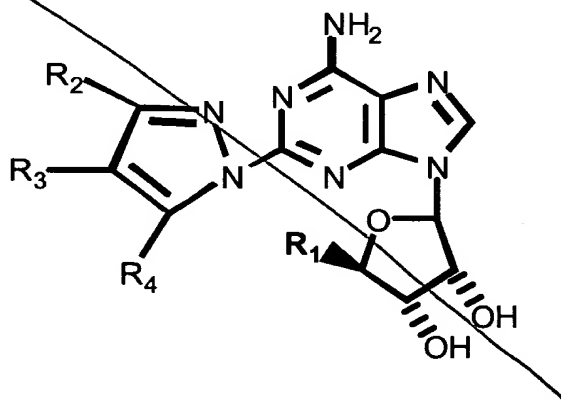
SUMMARY OF THE INVENTION

In one aspect, this invention includes 2-adenosine N-pyrazole compositions that are useful A_{2A} receptor agonists.

In another aspect, this invention includes pharmaceutical compositions including 2-adenosine N-pyrazole that are well tolerated with few side effects.

Still another aspect of this invention are N-pyrazole compositions that can be easily used in conjunction with radioactive imaging agents to facilitate coronary imaging.

In one embodiment, this invention includes 2-adenosine N-pyrazole compositions having the following formula:



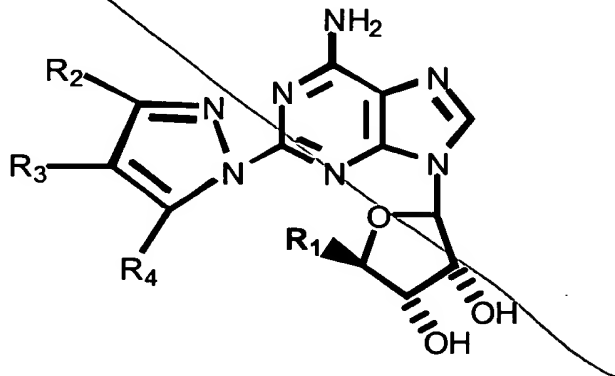
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In another embodiment, this invention includes methods for using compositions of this invention to stimulate coronary vasodilatation in mammals, and especially in humans, for stressing the heart induced steal situation for purposes of imaging the heart.

In still another embodiment, this invention is a pharmaceutical composition of matter comprising one or more compositions of this invention and one or more pharmaceutical excipients.

DESCRIPTION OF THE CURRENT EMBODIMENT

Subt
a2
This invention includes a class of 2-adenosine N-pyrazole having the formula:



5 wherein $R^1 = \text{CH}_2\text{OH}$, $-\text{CONR}_5\text{R}_6$;

R^3 is independently selected from the group consisting of C_{1-15} alkyl, halo, NO_2 , CF_3 , CN , OR^{20} , SR^{20} , $\text{N}(\text{R}^{20})_2$, $\text{S}(\text{O})\text{R}^{22}$, SO_2R^{22} , $\text{SO}_2\text{N}(\text{R}^{20})_2$, $\text{SO}_2\text{NR}^{20}\text{COR}^{22}$, $\text{SO}_2\text{NR}^{20}\text{CO}_2\text{R}^{22}$, $\text{SO}_2\text{NR}^{20}\text{CON}(\text{R}^{20})_2$, $\text{N}(\text{R}^{20})_2\text{NR}^{20}\text{COR}^{22}$, $\text{NR}^{20}\text{CO}_2\text{R}^{22}$, $\text{NR}^{20}\text{CON}(\text{R}^{20})_2$, $\text{NR}^{20}\text{C}(\text{NR}^{20})\text{NHR}^{23}$, COR^{20} , CO_2R^{20} , $\text{CON}(\text{R}^{20})_2$, $\text{CONR}^{20}\text{SO}_2\text{R}^{22}$, $\text{NR}^{20}\text{SO}_2\text{R}^{22}$, $\text{SO}_2\text{NR}^{20}\text{CO}_2\text{R}^{22}$, $\text{OCONR}^{20}\text{SO}_2\text{R}^{22}$, $\text{OC}(\text{O})\text{R}^{20}$, $\text{C}(\text{O})\text{OCH}_2\text{OC}(\text{O})\text{R}^{20}$, and $\text{OCON}(\text{R}^{20})_2$, $-\text{CONR}^7\text{R}^8$, C_{2-15} alkenyl, C_{2-15} alkynyl, heterocyclyl, aryl, and heteroaryl, wherein the alkyl, alkenyl, alkynyl, aryl, heterocyclyl and heteroaryl substituents are optionally substituted with from 1 to 3 substituents independently selected from the group consisting of halo, alkyl, NO_2 , heterocyclyl, aryl, heteroaryl, CF_3 , CN , OR^{20} , SR^{20} , $\text{N}(\text{R}^{20})_2$, $\text{S}(\text{O})\text{R}^{22}$, SO_2R^{22} , $\text{SO}_2\text{N}(\text{R}^{20})_2$, $\text{SO}_2\text{NR}^{20}\text{COR}^{22}$, $\text{SO}_2\text{NR}^{20}\text{CO}_2\text{R}^{22}$, $\text{SO}_2\text{NR}^{20}\text{CON}(\text{R}^{20})_2$, $\text{N}(\text{R}^{20})_2\text{NR}^{20}\text{COR}^{22}$, $\text{NR}^{20}\text{CO}_2\text{R}^{22}$, $\text{NR}^{20}\text{CON}(\text{R}^{20})_2$, $\text{NR}^{20}\text{C}(\text{NR}^{20})\text{NHR}^{23}$, COR^{20} , CO_2R^{20} , $\text{CON}(\text{R}^{20})_2$, $\text{CONR}^{20}\text{SO}_2\text{R}^{22}$, $\text{NR}^{20}\text{SO}_2\text{R}^{22}$, $\text{SO}_2\text{NR}^{20}\text{CO}_2\text{R}^{22}$, $\text{OCONR}^{20}\text{SO}_2\text{R}^{22}$, $\text{OC}(\text{O})\text{R}^{20}$, $\text{C}(\text{O})\text{OCH}_2\text{OC}(\text{O})\text{R}^{20}$, and $\text{OCON}(\text{R}^{20})_2$ and wherein the optional substituted heteroaryl, aryl, and heterocyclyl substituents are optionally substituted with halo, NO_2 , alkyl, CF_3 , amino, mono- or di- alkylamino, alkyl or aryl or heteroaryl amide, NCOR^{22} , $\text{NR}^{20}\text{SO}_2\text{R}^{22}$, COR^{20} , CO_2R^{20} , $\text{CON}(\text{R}^{20})_2$, $\text{NR}^{20}\text{CON}(\text{R}^{20})_2$, $\text{OC}(\text{O})\text{R}^{20}$, $\text{OC}(\text{O})\text{N}(\text{R}^{20})_2$, SR^{20} , $\text{S}(\text{O})\text{R}^{22}$,

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SO_2R^{22} , $\text{SO}_2\text{N}(\text{R}^{20})_2$, CN , or OR^{20} ;

R^5 and R^6 are each individually selected from H, and $\text{C}_1\text{-C}_{15}$ alkyl that is optionally substituted with from 1 to 2 substituents independently selected from the group of halo, NO_2 , heterocyclyl, aryl, heteroaryl, CF_3 , CN , OR^{20} , SR^{20} , $\text{N}(\text{R}^{20})_2$, $\text{S}(\text{O})\text{R}^{22}$, SO_2R^{22} , $\text{SO}_2\text{N}(\text{R}^{20})_2$, $\text{SO}_2\text{NR}^{20}\text{COR}^{22}$, $\text{SO}_2\text{NR}^{20}\text{CO}_2\text{R}^{22}$, $\text{SO}_2\text{NR}^{20}\text{CON}(\text{R}^{20})_2$, $\text{N}(\text{R}^{20})_2\text{NR}^{20}\text{COR}^{22}$, $\text{NR}^{20}\text{CO}_2\text{R}^{22}$, $\text{NR}^{20}\text{CON}(\text{R}^{20})_2$, $\text{NR}^{20}\text{C}(\text{NR}^{20})\text{NHR}^{23}$, COR^{20} , CO_2R^{20} , $\text{CON}(\text{R}^{20})_2$, $\text{CONR}^{20}\text{SO}_2\text{R}^{22}$, $\text{NR}^{20}\text{SO}_2\text{R}^{22}$, $\text{SO}_2\text{NR}^{20}\text{CO}_2\text{R}^{22}$, $\text{OCONR}^{20}\text{SO}_2\text{R}^{22}$, $\text{OC}(\text{O})\text{R}^{20}$, $\text{C}(\text{O})\text{OCH}_2\text{OC}(\text{O})\text{R}^{20}$, and $\text{OCON}(\text{R}^{20})_2$ wherein each optional substituted heteroaryl, aryl, and heterocyclyl substituent is optionally substituted with halo, NO_2 , alkyl, CF_3 , amino, monoalkylamino, dialkylamino, alkylamide, arylamide, heteroaryl amide, NCOR^{22} , $\text{NR}^{20}\text{SO}_2\text{R}^{22}$, COR^{20} , CO_2R^{20} , $\text{CON}(\text{R}^{20})_2$, $\text{NR}^{20}\text{CON}(\text{R}^{20})_2$, $\text{OC}(\text{O})\text{R}^{20}$, $\text{OC}(\text{O})\text{N}(\text{R}^{20})_2$, SR^{20} , $\text{S}(\text{O})\text{R}^{22}$, SO_2R^{22} , $\text{SO}_2\text{N}(\text{R}^{20})_2$, CN , and OR^{20} ;

R^7 is selected from the group consisting of hydrogen, C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl, heterocyclyl, aryl and heteroaryl, wherein the alkyl, alkenyl, alkynyl, aryl, heterocyclyl and heteroaryl substituents are optionally substituted with from 1 to 3 substituents independently selected from the group of halo, NO_2 , heterocyclyl, aryl, heteroaryl, CF_3 , CN , OR^{20} , SR^{20} , $\text{N}(\text{R}^{20})_2$, $\text{S}(\text{O})\text{R}^{22}$, SO_2R^{22} , $\text{SO}_2\text{N}(\text{R}^{20})_2$, $\text{SO}_2\text{NR}^{20}\text{COR}^{22}$, $\text{SO}_2\text{NR}^{20}\text{CO}_2\text{R}^{22}$, $\text{SO}_2\text{NR}^{20}\text{CON}(\text{R}^{20})_2$, $\text{N}(\text{R}^{20})_2\text{NR}^{20}\text{COR}^{22}$, $\text{NR}^{20}\text{CO}_2\text{R}^{22}$, $\text{NR}^{20}\text{CON}(\text{R}^{20})_2$, $\text{NR}^{20}\text{C}(\text{NR}^{20})\text{NHR}^{23}$, COR^{20} , CO_2R^{20} , $\text{CON}(\text{R}^{20})_2$, $\text{CONR}^{20}\text{SO}_2\text{R}^{22}$, $\text{NR}^{20}\text{SO}_2\text{R}^{22}$, $\text{SO}_2\text{NR}^{20}\text{CO}_2\text{R}^{22}$, $\text{OCONR}^{20}\text{SO}_2\text{R}^{22}$, $\text{OC}(\text{O})\text{R}^{20}$, $\text{C}(\text{O})\text{OCH}_2\text{OC}(\text{O})\text{R}^{20}$ and $\text{OCON}(\text{R}^{20})_2$ and wherein each optional substituted heteroaryl, aryl and heterocyclyl substituent is optionally substituted with halo, NO_2 , alkyl, CF_3 , amino, mono- or di- alkylamino, alkyl or aryl or heteroaryl amide, NCOR^{22} , $\text{NR}^{20}\text{SO}_2\text{R}^{22}$, COR^{20} , CO_2R^{20} , $\text{CON}(\text{R}^{20})_2$, $\text{NR}^{20}\text{CON}(\text{R}^{20})_2$, $\text{OC}(\text{O})\text{R}^{20}$, $\text{OC}(\text{O})\text{N}(\text{R}^{20})_2$, SR^{20} , $\text{S}(\text{O})\text{R}^{22}$, SO_2R^{22} , $\text{SO}_2\text{N}(\text{R}^{20})_2$, CN , and OR^{20} ;

R^8 is selected from the group consisting of hydrogen, C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl, heterocyclyl, aryl, and heteroaryl, wherein the alkyl, alkenyl, alkynyl, aryl,

heterocyclyl, and heteroaryl substituents are optionally substituted with from 1 to 3 substituents independently selected from the group consisting of halo, NO₂, heterocyclyl, aryl, heteroaryl, CF₃, CN, OR²⁰, SR²⁰, N(R²⁰)₂, S(O)R²², SO₂R²², SO₂N(R²⁰)₂, SO₂NR²⁰COR²², SO₂NR²⁰CO₂R²², SO₂NR²⁰CON(R²⁰)₂, N(R²⁰)₂ NR²⁰COR²², NR²⁰CO₂R²², NR²⁰CON(R²⁰)₂,
 5 NR²⁰C(NR²⁰)NHR²³, COR²⁰, CO₂R²⁰, CON(R²⁰)₂, CONR²⁰SO₂R²², NR²⁰SO₂R²², SO₂NR²⁰CO₂R²², OCONR²⁰SO₂R²², OC(O)R²⁰, C(O)OCH₂OC(O)R²⁰, and OCON(R²⁰)₂ and wherein each optional substituted heteroaryl, aryl, and heterocyclyl substituent is optionally substituted with halo, NO₂, alkyl, CF₃, amino, mono- or di- alkylamino, alkyl or aryl or heteroaryl amide, NCOR²², NR²⁰SO₂R²², COR²⁰, CO₂R²⁰, CON(R²⁰)₂, NR²⁰CON(R²⁰)₂,
 10 OC(O)R²⁰, OC(O)N(R²⁰)₂, SR²⁰, S(O)R²², SO₂R²², SO₂N(R²⁰)₂, CN, and OR²⁰;

R²⁰ is selected from the group consisting of H, C₁₋₁₅ alkyl, C₂₋₁₅ alkenyl, C₂₋₁₅ alkynyl, heterocyclyl, aryl, and heteroaryl, wherein the alkyl, alkenyl, alkynyl, heterocyclyl, aryl, and heteroaryl substituents are optionally substituted with from 1 to 3 substituents independently selected from halo, alkyl, mono- or dialkylamino, alkyl or aryl or heteroaryl amide, CN, O-C₁₋₆ alkyl, CF₃, aryl, and heteroaryl;
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R²² is selected from the group consisting of C₁₋₁₅ alkyl, C₂₋₁₅ alkenyl, C₂₋₁₅ alkynyl, heterocyclyl, aryl, and heteroaryl, wherein the alkyl, alkenyl, alkynyl, heterocyclyl, aryl, and heteroaryl substituents are optionally substituted with from 1 to 3 substituents independently selected from halo, alkyl, mono- or dialkylamino, alkyl or aryl or heteroaryl amide, CN, O-C₁₋₆ alkyl, CF₃, aryl, and heteroaryl; and
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wherein R² and R⁴ are selected from the group consisting of H, C₁₋₆ alkyl and aryl, wherein the alkyl and aryl substituents are optionally substituted with halo, CN, CF₃, OR²⁰ and N(R²⁰)₂ with the proviso that when R² is not hydrogen then R⁴ is hydrogen, and when R⁴ is not hydrogen then R² is hydrogen.

25 In preferred compositions of this invention, R³ is selected from the group consisting of

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C_{1-15} alkyl, halo, CF_3 , CN, OR^{20} , SR^{20} , $S(O)R^{22}$, SO_2R^{22} , $SO_2N(R^{20})_2$, COR^{20} , CO_2R^{20} , -
 $CONR^7R^8$, aryl and heteroaryl wherein the alkyl, aryl and heteroaryl substituents are
 optionally substituted with from 1 to 3 substituents independently selected from the group
 consisting of halo, aryl, heteroaryl, CF_3 , CN, OR^{20} , SR^{20} , $S(O)R^{22}$, SO_2R^{22} , $SO_2N(R^{20})_2$, COR^{20} ,
 5 CO_2R^{20} or $CON(R^{20})_2$, and each optional heteroaryl and aryl substituent is optionally
 substituted with halo, alkyl, CF_3 , CN, and OR^{20} ; R^5 and R^6 are independently selected from the
 group of H and C_1 - C_{15} alkyl including one optional aryl substituent and each optional aryl
 substituent that is optionally substituted with halo or CF_3 ; R^7 is selected from the group
 consisting of C_{1-15} alkyl, C_{2-15} alkynyl, aryl, and heteroaryl, wherein the alkyl, alkynyl, aryl,
 10 and heteroaryl substituents are optionally substituted with from 1 to 3 substituents
 independently selected from the group consisting of halo, aryl, heteroaryl, CF_3 , CN, OR^{20} , and
 each optional heteroaryl and aryl substituent is optionally substituted with halo, alkyl, CF_3 ,
 CN, or OR^{20} ; R^8 is selected from the group consisting of hydrogen and C_{1-15} alkyl; R^{20} is
 15 selected from the group consisting of H, C_{1-4} alkyl and aryl, wherein alkyl and aryl
 substituents are optionally substituted with one alkyl substituent; and R^{22} is selected from the
 group consisting of C_{1-4} alkyl and aryl which are each optionally substituted with from 1 to 3
 alkyl group.

In more preferred compositions, R^1 is CH_2OH ; R^3 is selected from the group consisting
 of CO_2R^{20} , $-CONR^7R^8$ and aryl where the aryl substituent is optionally substituted with from
 20 1 to 2 substituents independently selected from the group consisting of halo, C_{1-6} alkyl, CF_3 ,
 and OR^{20} ; R^7 is selected from the group consisting of hydrogen, C_{1-8} alkyl and aryl, where the
 alkyl and aryl substituents are optionally substituted with one substituent selected from the
 group consisting of halo, aryl, CF_3 , CN, OR^{20} and wherein each optional aryl substituent is
 optionally substituted with halo, alkyl, CF_3 , CN, and OR^{20} ; R^8 is selected from the group
 25 consisting of hydrogen and C_{1-8} alkyl; and R^{20} is selected from hydrogen and C_{1-4} alkyl.



In a still more preferred embodiment, $R^1 = CH_2OH$; R^3 is selected from the group consisting of CO_2R^{20} , $-CONR^7R^8$, and aryl that is optionally substituted with one substituent selected from the group consisting of halo, C_{1-3} alkyl and OR^{20} ; R^7 is selected from hydrogen, and C_{1-3} alkyl; R^8 is hydrogen; and R^{20} is selected from hydrogen and C_{1-4} alkyl. In this preferred embodiment, R^3 is most preferably selected from $-CO_2Et$ and $-CONHEt$.

In another still more preferred embodiment, $R^1 = -CONHEt$, R^3 is selected from the group consisting of CO_2R^{20} , $-CONR^7R^8$, and aryl in that aryl is optionally substituted with from 1 to 2 substituents independently selected from the group consisting of halo, C_{1-3} alkyl, CF_3 or OR^{20} ; R^7 is selected from the group consisting of hydrogen, and C_{1-8} alkyl that is optionally substituted with one substituent selected from the group consisting of halo, CF_3 , CN or OR^{20} ; R^8 is selected from the group consisting of hydrogen and C_{1-3} alkyl; and R^{20} is selected from the group consisting of hydrogen and C_{1-4} alkyl. In this more preferred embodiment, R^8 is preferably hydrogen, R^7 is preferably selected from the group consisting of hydrogen, and C_{1-3} , and R^{20} is preferably selected from the group consisting of hydrogen and C_{1-4} alkyl.

In a most preferred embodiment, the composition of this invention is selected from ethyl 1-{9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-aminopurin-2-yl}pyrazole-4-carboxylate, (4S,2R,3R,5R)-2-{6-amino-2-[4-(4-chlorophenyl)pyrazolyl]purin-9-yl}-5-(hydroxymethyl)oxolane-3,4-diol, (4S,2R,3R,5R)-2-{6-amino-2-[4-(4-methoxyphenyl)pyrazolyl]purin-9-yl}-5-(hydroxymethyl)oxolane-3,4-diol, (4S,2R,3R,5R)-2-{6-amino-2-[4-(4-methylphenyl)pyrazolyl]purin-9-yl}-5-(hydroxymethyl)oxolane-3,4-diol, (1-{9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-aminopurin-2-yl}pyrazol-4-yl)-N-methylcarboxamide, 1-{9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-aminopurin-2-yl}pyrazole-4-carboxylic acid, and mixtures thereof.

The following definitions apply to terms as used herein.

"Halo" or "Halogen" - alone or in combination means all halogens, that is, chloro (Cl), fluoro (F), bromo (Br), iodo (I).

"Hydroxyl" refers to the group -OH.

5 "Thiol" or "mercapto" refers to the group -SH.

"Alkyl" - alone or in combination means an alkane-derived radical containing from 1 to 20, preferably 1 to 15, carbon atoms (unless specifically defined). It is a straight chain alkyl, branched alkyl or cycloalkyl. Preferably, straight or branched alkyl groups containing from 1-15, more preferably 1 to 8, even more preferably 1-6, yet more preferably 1-4 and most preferably 1-2, carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl and the like. The term "lower alkyl" is used herein to describe the straight chain alkyl groups described immediately above. Preferably, cycloalkyl groups are monocyclic, bicyclic or tricyclic ring systems of 3-8, more preferably 3-6, ring members per ring, such as cyclopropyl, cyclopentyl, cyclohexyl, adamantyl and the like. Alkyl also includes a straight chain or
15 branched alkyl group that contains or is interrupted by a cycloalkyl portion. The straight chain or branched alkyl group is attached at any available point to produce a stable compound. Examples of this include, but are not limited to, 4-(isopropyl)-cyclohexylethyl or 2-methyl-cyclopropylpentyl. A substituted alkyl is a straight chain alkyl, branched alkyl, or cycloalkyl group defined previously, independently substituted with 1 to 3 groups or substituents of halo,
20 hydroxy, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, acyloxy, aryloxy, heteroaryloxy, amino optionally mono- or di-substituted with alkyl, aryl or heteroaryl groups, amidino, urea optionally substituted with alkyl, aryl, heteroaryl or heterocyclyl groups, aminosulfonyl optionally N-mono- or N,N-di-substituted with alkyl, aryl or heteroaryl groups, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, alkylcarbonylamino,
25 arylcarbonylamino, heteroarylcarbonylamino, or the like.

"Alkenyl" - alone or in combination means a straight, branched, or cyclic hydrocarbon containing 2-20, preferably 2-17, more preferably 2-10, even more preferably 2-8, most preferably 2-4, carbon atoms and at least one, preferably 1-3, more preferably 1-2, most preferably one, carbon to carbon double bond. In the case of a cycloalkyl group, conjugation of more than one carbon to carbon double bond is not such as to confer aromaticity to the ring. Carbon to carbon double bonds may be either contained within a cycloalkyl portion, with the exception of cyclopropyl, or within a straight chain or branched portion. Examples of alkenyl groups include ethenyl, propenyl, isopropenyl, butenyl, cyclohexenyl, cyclohexenylalkyl and the like. A substituted alkenyl is the straight chain alkenyl, branched alkenyl or cycloalkenyl group defined previously, independently substituted with 1 to 3 groups or substituents of halo, hydroxy, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, acyloxy, aryloxy, heteroaryloxy, amino optionally mono- or di-substituted with alkyl, aryl or heteroaryl groups, amidino, urea optionally substituted with alkyl, aryl, heteroaryl or heterocyclyl groups, aminosulfonyl optionally N-mono- or N,N-di-substituted with alkyl, aryl or heteroaryl groups, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, carboxy, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, or the like attached at any available point to produce a stable compound.

"Alkynyl" - alone or in combination means a straight or branched hydrocarbon containing 2-20, preferably 2-17, more preferably 2-10, even more preferably 2-8, most preferably 2-4, carbon atoms containing at least one, preferably one, carbon to carbon triple bond. Examples of alkynyl groups include ethynyl, propynyl, butynyl and the like. A substituted alkynyl refers to the straight chain alkynyl or branched alkenyl defined previously, independently substituted with 1 to 3 groups or substituents of halo, hydroxy, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, acyloxy, aryloxy, heteroaryloxy, amino optionally

mono- or di-substituted with alkyl, aryl or heteroaryl groups, amidino, urea optionally substituted with alkyl, aryl, heteroaryl or heterocyclyl groups, aminosulfonyl optionally N-mono- or N,N-di-substituted with alkyl, aryl or heteroaryl groups, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, or the like attached at any available point to produce a stable compound.

“Alkyl alkenyl” refers to a group $-R-CR'=CR''R'''$, where R is lower alkyl, or substituted lower alkyl, R', R'', R''' may independently be hydrogen, halogen, lower alkyl, substituted lower alkyl, acyl, aryl, substituted aryl, hetaryl, or substituted hetaryl as defined below.

“Alkyl alkynyl” refers to a groups $-RC\equiv CR'$ where R is lower alkyl or substituted lower alkyl, R' is hydrogen, lower alkyl, substituted lower alkyl, acyl, aryl, substituted aryl, hetaryl, or substituted hetaryl as defined below.

“Alkoxy” denotes the group $-OR$, where R is lower alkyl, substituted lower alkyl, acyl, aryl, substituted aryl, aralkyl, substituted aralkyl, heteroalkyl, heteroarylalkyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, or substituted cycloheteroalkyl as defined.

“Alkylthio” denotes the group $-SR$, $-S(O)_{n=1-2}-R$, where R is lower alkyl, substituted lower alkyl, aryl, substituted aryl, aralkyl or substituted aralkyl as defined herein.

“Acyl” denotes groups $-C(O)R$, where R is hydrogen, lower alkyl substituted lower alkyl, aryl, substituted aryl and the like as defined herein.

“Aryloxy” denotes groups $-OAr$, where Ar is an aryl, substituted aryl, heteroaryl, or substituted heteroaryl group as defined herein.

“Amino” denotes the group NRR' , where R and R' may independently be hydrogen, lower alkyl, substituted lower alkyl, aryl, substituted aryl, hetaryl, or substituted hetaryl as defined herein or acyl.

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"Amido" denotes the group $-C(O)NRR'$, where R and R' may independently be hydrogen, lower alkyl, substituted lower alkyl, aryl, substituted aryl, hetaryl, substituted hetaryl as defined herein.

"Carboxyl" denotes the group $-C(O)OR$, where R is hydrogen, lower alkyl, substituted lower alkyl, aryl, substituted aryl, hetaryl, and substituted hetaryl as defined herein.

"Aryl" - alone or in combination means phenyl or naphthyl optionally carbocyclic fused with a cycloalkyl of preferably 5-7, more preferably 5-6, ring members and/or optionally substituted with 1 to 3 groups or substituents of halo, hydroxy, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, acyloxy, aryloxy, heteroaryloxy, amino optionally mono- or di-substituted with alkyl, aryl or heteroaryl groups, amidino, urea optionally substituted with alkyl, aryl, heteroaryl or heterocyclyl groups, aminosulfonyl optionally N-mono- or N,N-di-substituted with alkyl, aryl or heteroaryl groups, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, or the like.

"Substituted aryl" refers to aryl optionally substituted with one or more functional groups, *e.g.*, halogen, lower alkyl, lower alkoxy, alkylthio, acetylene, amino, amido, carboxyl, hydroxyl, aryl, aryloxy, heterocycle, hetaryl, substituted hetaryl, nitro, cyano, thiol, sulfamido and the like.

"Heterocycle" refers to a saturated, unsaturated, or aromatic carbocyclic group having a single ring (*e.g.*, morpholino, pyridyl or furyl) or multiple condensed rings (*e.g.*, naphthpyridyl, quinoxalyl, quinolinyl, indolizinyll or benzo[b]thienyl) and having at least one hetero atom, such as N, O or S, within the ring, which can optionally be unsubstituted or substituted with, *e.g.*, halogen, lower alkyl, lower alkoxy, alkylthio, acetylene, amino, amido, carboxyl, hydroxyl, aryl, aryloxy, heterocycle, hetaryl, substituted hetaryl, nitro, cyano, thiol, sulfamido and the like.

"Heteroaryl" - alone or in combination means a monocyclic aromatic ring structure containing 5 or 6 ring atoms, or a bicyclic aromatic group having 8 to 10 atoms, containing one or more, preferably 1-4, more preferably 1-3, even more preferably 1-2, heteroatoms independently selected from the group O, S, and N, and optionally substituted with 1 to 3 groups or substituents of halo, hydroxy, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, acyloxy, aryloxy, heteroaryloxy, amino optionally mono- or di-substituted with alkyl, aryl or heteroaryl groups, amidino, urea optionally substituted with alkyl, aryl, heteroaryl or heterocyclyl groups, aminosulfonyl optionally N-mono- or N,N-di-substituted with alkyl, aryl or heteroaryl groups, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, or the like. Heteroaryl is also intended to include oxidized S or N, such as sulfinyl, sulfonyl and N-oxide of a tertiary ring nitrogen. A carbon or nitrogen atom is the point of attachment of the heteroaryl ring structure such that a stable aromatic ring is retained. Examples of heteroaryl groups are pyridinyl, pyridazinyl, pyrazinyl, quinazolinyl, purinyl, indolyl, quinolinyl, pyrimidinyl, pyrrolyl, oxazolyl, thiazolyl, thienyl, isoxazolyl, oxathiadiazolyl, isothiazolyl, tetrazolyl, imidazolyl, triazinyl, furanyl, benzofuryl, indolyl and the like. A substituted heteroaryl contains a substituent attached at an available carbon or nitrogen to produce a stable compound.

"Heterocyclyl" - alone or in combination means a non-aromatic cycloalkyl group having from 5 to 10 atoms in which from 1 to 3 carbon atoms in the ring are replaced by heteroatoms of O, S or N, and are optionally benzo fused or fused heteroaryl of 5-6 ring members and/or are optionally substituted as in the case of cycloalkyl. Heterocyclyl is also intended to include oxidized S or N, such as sulfinyl, sulfonyl and N-oxide of a tertiary ring nitrogen. The point of attachment is at a carbon or nitrogen atom. Examples of heterocyclyl groups are tetrahydrofuranyl, dihydropyridinyl, piperidinyl, pyrrolidinyl, piperazinyl,

dihydrobenzofuryl, dihydroindolyl, and the like. A substituted heterocyclyl contains a substituent nitrogen attached at an available carbon or nitrogen to produce a stable compound.

"Substituted heteroaryl" refers to a heterocycle optionally mono or poly substituted with one or more functional groups, *e.g.*, halogen, lower alkyl, lower alkoxy, alkylthio, acetylene, amino, amido, carboxyl, hydroxyl, aryl, aryloxy, heterocycle, substituted heterocycle, hetaryl, substituted hetaryl, nitro, cyano, thiol, sulfamido and the like.

"Aralkyl" refers to the group -R-Ar where Ar is an aryl group and R is lower alkyl or substituted lower alkyl group. Aryl groups can optionally be unsubstituted or substituted with, *e.g.*, halogen, lower alkyl, alkoxy, alkylthio, acetylene, amino, amido, carboxyl, hydroxyl, aryl, aryloxy, heterocycle, substituted heterocycle, hetaryl, substituted hetaryl, nitro, cyano, thiol, sulfamido and the like.

"Heteroalkyl" refers to the group -R-Het where Het is a heterocycle group and R is a lower alkyl group. Heteroalkyl groups can optionally be unsubstituted or substituted with *e.g.*, halogen, lower alkyl, lower alkoxy, alkylthio, acetylene, amino, amido, carboxyl, aryl, aryloxy, heterocycle, substituted heterocycle, hetaryl, substituted hetaryl, nitro, cyano, thiol, sulfamido and the like.

"Heteroarylalkyl" refers to the group -R-HetAr where HetAr is an heteroaryl group and R lower alkyl or substituted lower alkyl. Heteroarylalkyl groups can optionally be unsubstituted or substituted with, *e.g.*, halogen, lower alkyl, substituted lower alkyl, alkoxy, alkylthio, acetylene, aryl, aryloxy, heterocycle, substituted heterocycle, hetaryl, substituted hetaryl, nitro, cyano, thiol, sulfamido and the like.

"Cycloalkyl" refers to a divalent cyclic or polycyclic alkyl group containing 3 to 15 carbon atoms.

"Substituted cycloalkyl" refers to a cycloalkyl group comprising one or more substituents with, *e.g.*, halogen, lower alkyl, substituted lower alkyl, alkoxy, alkylthio,

acetylene, aryl, aryloxy, heterocycle, substituted heterocycle, hetaryl, substituted hetaryl, nitro, cyano, thiol, sulfamido and the like.

"Cycloheteroalkyl" refers to a cycloalkyl group wherein one or more of the ring carbon atoms is replaced with a heteroatom (*e.g.*, N, O, S or P).

5 "Substituted cycloheteroalkyl" refers to a cycloheteroalkyl group as herein defined which contains one or more substituents, such as halogen, lower alkyl, lower alkoxy, alkylthio, acetylene, amino, amido, carboxyl, hydroxyl, aryl, aryloxy, heterocycle, substituted heterocycle, hetaryl, substituted hetaryl, nitro, cyano, thiol, sulfamido and the like.

10 "Alkyl cycloalkyl" denotes the group -R-cycloalkyl where cycloalkyl is a cycloalkyl group and R is a lower alkyl or substituted lower alkyl. Cycloalkyl groups can optionally be unsubstituted or substituted with *e.g.* halogen, lower alkyl, lower alkoxy, alkylthio, acetylene, amino, amido, carboxyl, hydroxyl, aryl, aryloxy, heterocycle, substituted heterocycle, hetaryl, substituted hetaryl, nitro, cyano, thiol, sulfamido and the like.

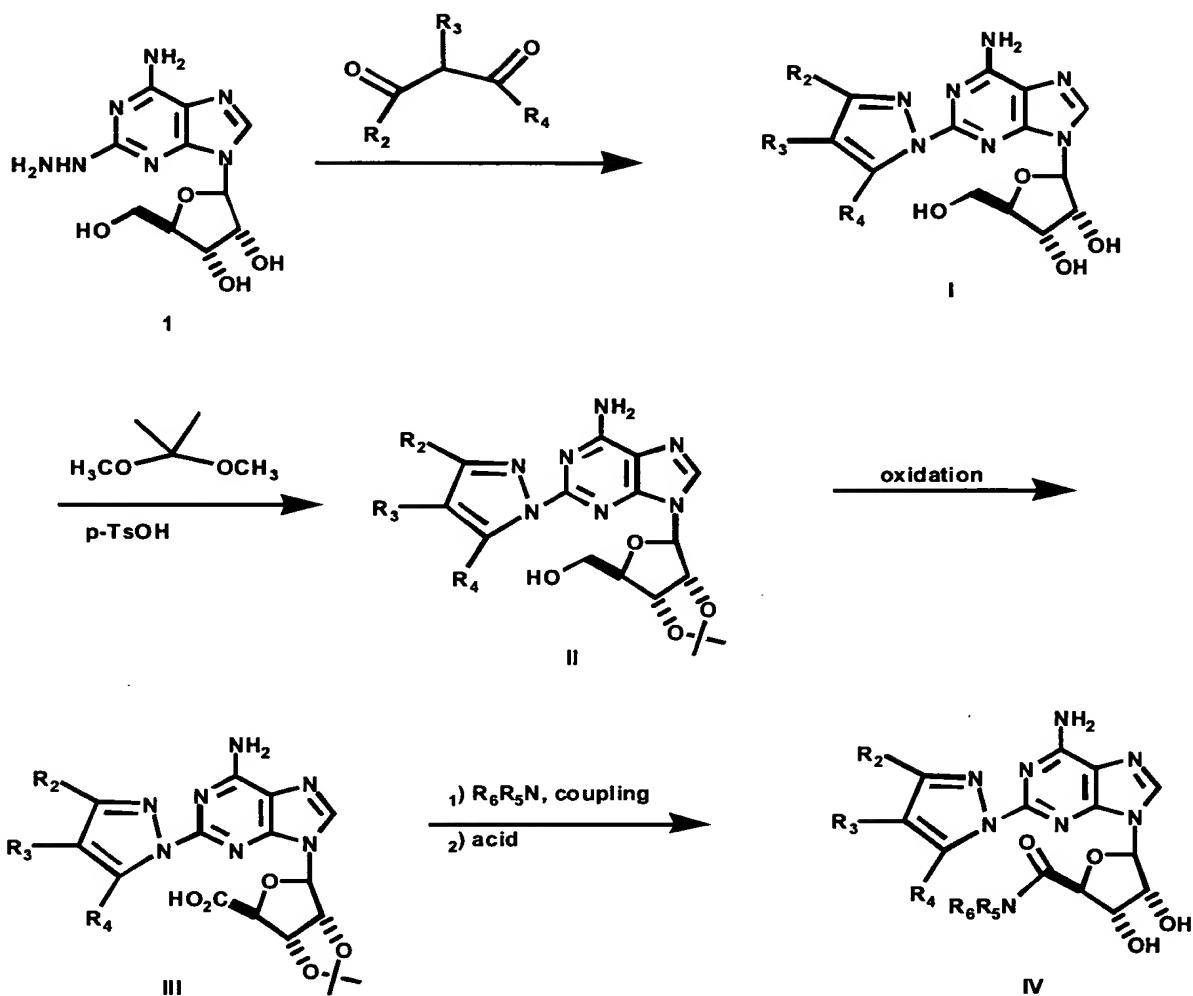
15 "Alkyl cycloheteroalkyl" denotes the group -R-cycloheteroalkyl where R is a lower alkyl or substituted lower alkyl. Cycloheteroalkyl groups can optionally be unsubstituted or substituted with *e.g.* halogen, lower alkyl, lower alkoxy, alkylthio, amino, amido, carboxyl, acetylene, hydroxyl, aryl, aryloxy, heterocycle, substituted heterocycle, hetaryl, substituted hetaryl, nitro, cyano, thiol, sulfamido and the like.

The compounds of this invention can be prepared as outlined in Schemes 1-4.

20 Compounds having the general formula IV can be prepared as shown in Scheme 1.

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Scheme 1.

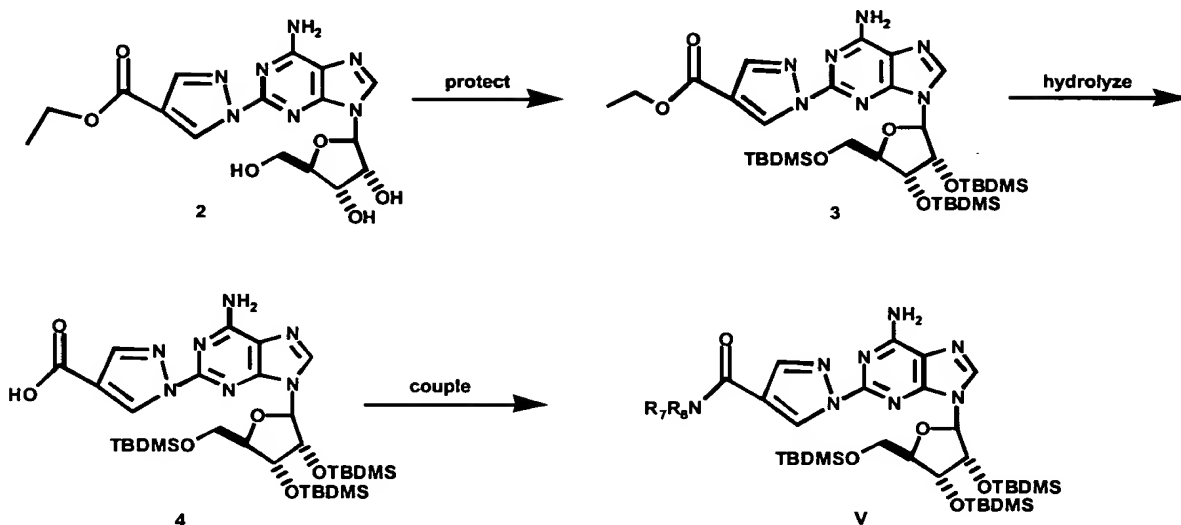


Compound I can be prepared by reacting compound 1 with appropriately substituted 1,3-dicarbonyl in a mixture of AcOH and MeOH at 80°C (Holzer et al., J. Heterocycl. Chem.

- 5 (1993) 30, 865). Compound II, which can be obtained by reacting compound I with 2,2-dimethoxypropane in the presence of an acid, can be oxidized to the carboxylic acid III, based on structurally similar compounds using potassium permanganate or pyridinium chlorochromate (M. Hudlicky, (1990) Oxidations in Organic Chemistry, ACS Monographs, American Chemical Society, Washington D. C.). Reaction of a primary or secondary amine
- 10 having the formula HNR^6R^7 , and compound III using DCC (M. Fujino et al., Chem. Pharm. Bull. (1974), 22, 1857), PyBOP (J. Martinez et al., J. Med. Chem. (1988) 28, 1874) or PyBrop
- 17

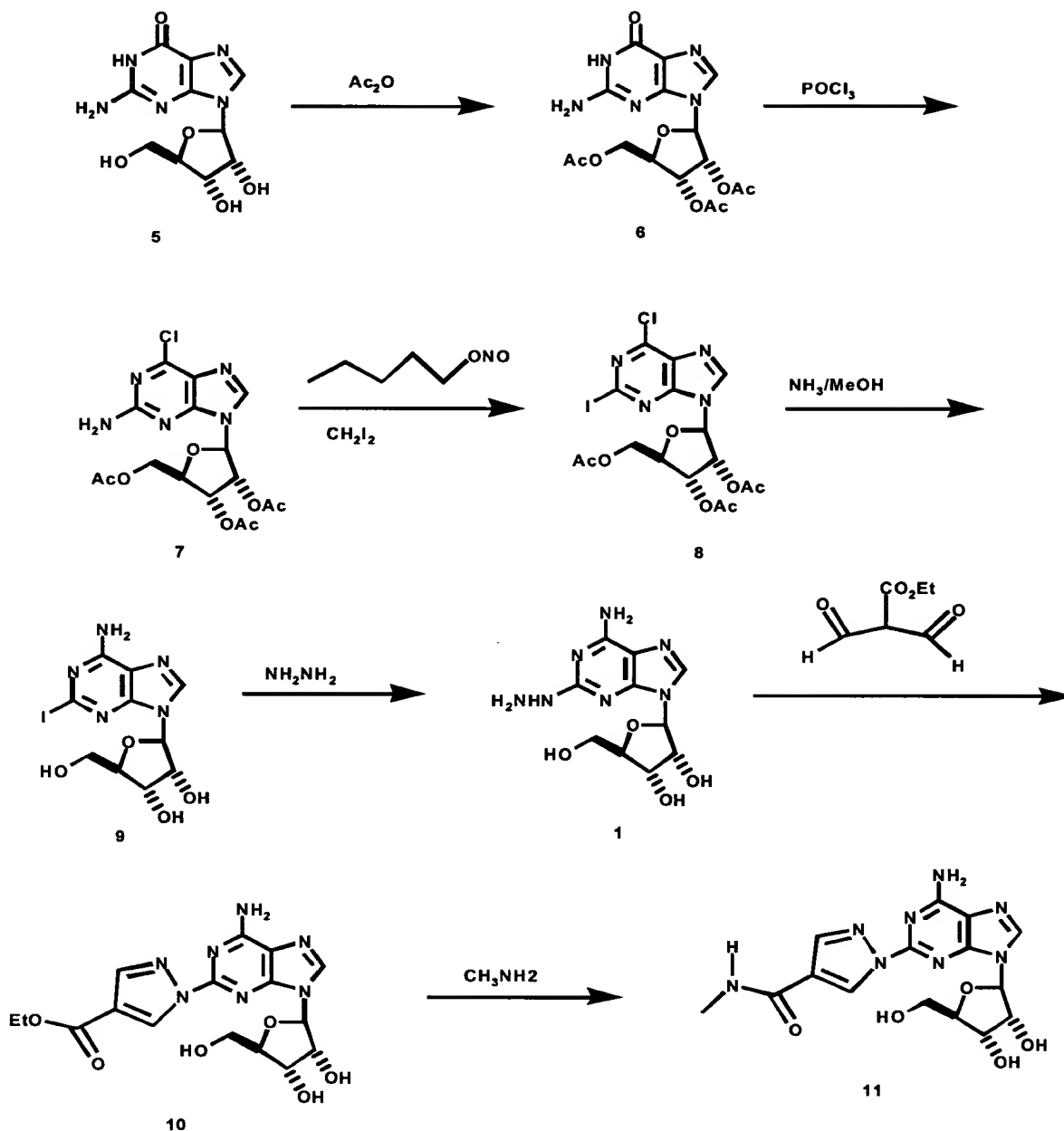
(J. Caste et al. Tetrahedron, (1991), 32, 1967) coupling conditions can afford compound IV.

Scheme 2.



Compound V can be prepared as shown in Scheme 2. The Tri TBDMS derivative 4 can be obtained by treating compound 2 with TBDMSCl and imidazole in DMF followed by hydrolysis of the ethyl ester using NaOH. Reaction of a primary or secondary amine with the formula HNR⁶R⁷, and compound 4 using DCC (M. Fujino et al., Chem. Pharm. Bull. (1974), 22, 1857), PyBOP (J. Martinez et al., J. Med. Chem. (1988) 28, 1874) or PyBrop (J. Caste et al. Tetrahedron, (1991), 32, 1967) coupling conditions can afford compound V.

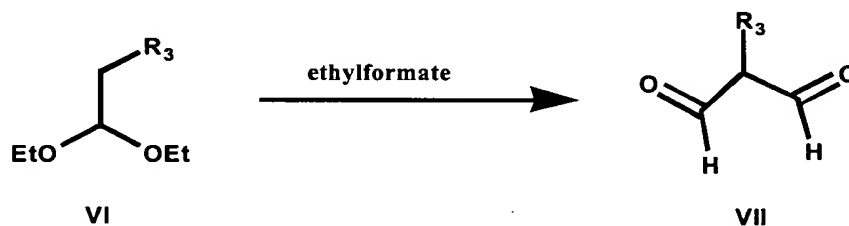
Scheme 3



A specific synthesis of compound 11 is illustrated in Scheme 3. Commercially available guanosine 5 was converted to the triacetate 6 as previously described (M. J. Robins and B. Uznanski, Can. J. Chem. (1981), 59, 2601-2607). Compound 7, prepared by following the literature procedure of Cerster et al. (J. F. Cerster, A. F. Lewis, and R.K. Robins, Org. Synthesis, 242-243), was converted to compound 9 in two steps as previously described (V.

Nair et al., J. Org. Chem., (1988), 53, 3051-3057). Compound 1 was obtained by reacting hydrazine hydrate with compound 9 in ethanol at 80°C. Condensation of compound 1 with ethoxycarbonylmalondialdehyde in a mixture of AcOH and MeOH at 80°C produced compound 10. Heating compound 10 in excess methylamine afforded compound 11.

5 **Scheme 4**



The synthesis of 1,3-dialdehyde VII is described in Scheme 4. Reaction of 3,3-diethoxypropionate or 3,3-diethoxypropionitrile or 1,1-diethoxy-2-nitroethane VI ($R_3 = \text{CO}_2\text{R}$, CN or NO_2) with ethyl or methyl formate in the presence of NaH can afford the dialdehyde VII (Y. Yamamoto et al., J. Org. Chem. (1989) 54, 4734).

Compounds of this invention are useful in conjunction with radioactive imaging agents to image coronary activity. The compounds of this invention are A_{2A} agonists that are believed to provide specific activation of adenosine A_{2A} receptors in the coronary vessels as opposed to adenosine A_1 receptors in the atrium and AV-node and/or A_{2B} receptors in peripheral vessels, thus avoiding undesirable side-effects. Upon administration in a therapeutic amount, the compositions of this invention cause coronary blood vessels to vasodilate to induce coronary steal wherein healthy coronary vessels steal blood from unhealthy vessels resulting in lack of blood flow to heart tissues. Lower doses of the A_{2A} agonists may provide beneficial coronary vasodilatation (less severe) in the treatment of chronic CAD.

As A_{2A} agonists, the compositions of this invention are also useful in adjunctive therapy with angioplasty to induce dilation, inhibit platelet aggregation, and as a general anti-

inflammatory agent. A_{2A} agonists, such as the compositions of this invention, can provide the therapeutic benefits described above by preventing neutrophil activation (Purinergic Approaches in Experimental Therapeutics K. A. Jacobson and M. F. Jarvis 1997 Wiley, New York). The compounds of this invention are also effective against a condition called no-reflow in which platelets and neutrophils aggregate and block a vessel. As A_{2A} agonists, the compositions of this invention are effective against no-reflow by preventing neutrophil and platelet activation (e.g., they are believed to prevent release of superoxide from neutrophils). As A_{2A} agonists, the compositions of this invention are also useful as cardioprotective agents through their anti-inflammatory action on neutrophils. Thus, in situations when the heart will go through an ischemic state such as a transplant, they will be useful.

This invention also includes pro-drugs of the above-identified A_{2A} agonists. A pro-drug is a drug which has been chemically modified and may be biological inactive at its site of action, but which will be degraded or modified by one or more enzymatic or *in vivo* processes to the bioactive form. The pro-drugs of this invention should have a different pharmacokinetic profile to the parent enabling improved absorption across the mucosal epithelium, better salt formulation and/or solubility and improved systemic stability. The above-identified compounds may be preferably modified at one or more of the hydroxyl groups. The modifications may be (1) ester or carbamate derivatives which may be cleaved by esterases or lipases, for example; (2) peptides which may be recognized by specific or non-specific proteinase; or (3) derivatives that accumulate at a site of action through membrane selection or a pro-drug form or modified pro-drug form, or any combination of (1) to (3) above.

The compositions may be administered orally, intravenously, through the epidermis or by any other means known in the art for administering a therapeutic agents. The method of treatment comprises the administration of an effective quantity of the chosen compound,

preferably dispersed in a pharmaceutical carrier. Dosage units of the active ingredient are generally selected from the range of 0.01 to 100 mg/kg, but will be readily determined by one skilled in the art depending upon the route of administration, age and condition of the patient. This dose is typically administered in a solution about 5 minutes to about an hour or more prior to coronary imaging. No unacceptable toxicological effects are expected when compounds of the invention are administered in accordance with the present invention.

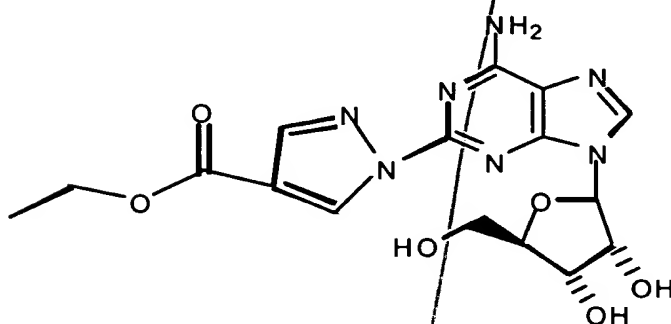
If the final compound of this invention contains a basic group, an acid addition salt may be prepared. Acid addition salts of the compounds are prepared in a standard manner in a suitable solvent from the parent compound and an excess of acid, such as hydrochloric, hydrobromic, sulfuric, phosphoric, acetic, maleic, succinic, or methanesulfonic. The hydrochloric salt form is especially useful. If the final compound contains an acidic group, cationic salts may be prepared. Typically the parent compound is treated with an excess of an alkaline reagent, such as hydroxide, carbonate or alkoxide, containing the appropriate cation. Cations such as Na^+ , K^+ , Ca^{+2} and NH_4^+ are examples of cations present in pharmaceutically acceptable salts. Certain of the compounds form inner salts or zwitterions which may also be acceptable.

Pharmaceutical compositions including the compounds of this invention, and/or derivatives thereof, may be formulated as solutions or lyophilized powders for parenteral administration. Powders may be reconstituted by addition of a suitable diluent or other pharmaceutically acceptable carrier prior to use. If used in liquid form the compositions of this invention are preferably incorporated into a buffered, isotonic, aqueous solution. Examples of suitable diluents are normal isotonic saline solution, standard 5% dextrose in water and buffered sodium or ammonium acetate solution. Such liquid formulations are suitable for parenteral administration, but may also be used for oral administration. It may be desirable to add excipients such as polyvinylpyrrolidinone, gelatin, hydroxycellulose,

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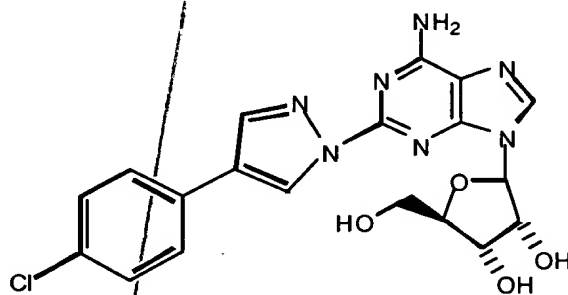
acacia, polyethylene glycol, mannitol, sodium chloride, sodium citrate or any other excipient known to one of skill in the art to pharmaceutical compositions including compounds of this invention. Alternatively, the pharmaceutical compounds may be encapsulated, tableted or prepared in an emulsion or syrup for oral administration. Pharmaceutically acceptable solid or liquid carriers may be added to enhance or stabilize the composition, or to facilitate preparation of the composition. Liquid carriers include syrup, peanut oil, olive oil, glycerin, saline, alcohols and water. Solid carriers include starch, lactose, calcium sulfate, dihydrate, teffa alba, magnesium stearate or stearic acid, talc, pectin, acacia, agar or gelatin. The carrier may also include a sustained release material such as glycerol monostearate or glycerol distearate, alone or with a wax. The amount of solid carrier varies but, preferably, will be between about 20 mg to about 1 gram per dosage unit. The pharmaceutical dosages are made using conventional techniques such as milling, mixing, granulation, and compressing, when necessary, for tablet forms; or milling, mixing and filling for hard gelatin capsule forms. When a liquid carrier is used, the preparation will be in the form of a syrup, elixir, emulsion or an aqueous or non-aqueous suspension. Such a liquid formulation may be administered directly or filled into a soft gelatin capsule. It is preferred that the compositions of this invention are administered as a solution either orally or intravenously.

The Examples which follow serve to illustrate this invention. The Examples are intended to in no way limit the scope of this invention, but are provided to show how to make and use the compounds of this invention. In the Examples, all temperatures are in degrees Centigrade.

Example 1

ethyl 11-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-aminopurin-2-ylpyrazole-4-carboxylate (12)

- 5 To a suspension of 2-hydrazinoadenosine (0.025 g, 0.08 mmol) in a 1:1 mixture of MeOH/AcOH was added (ethoxycarbonyl)malondialdehyde (0.019 g, 0.12 mmol) and the mixture was heated at 80°C for 3 h. The precipitate formed was collected by filtration and washed with EtOH and ether to afford 12. ¹HNMR (DMSO-d₆) δ 1.25 (t, 3 H), 3.5 (m, 1 H), 3.6 (m, 1 H), 3.8 (d, 1 H), 4.15 (d, 1 H), 4.55 (m, 1H), 5.0 (t, 1 H), 5.2 (d, 1 H), 5.5 (d, 1 H), 5.9 (d, 1H), 7.15-7.3 (m, 5 H), 7.8 (br s, 2 H), 8.1 (s, 1H), 8.4 (s, 1 H), 8.9 (s, 1H).
- 10

Example 2

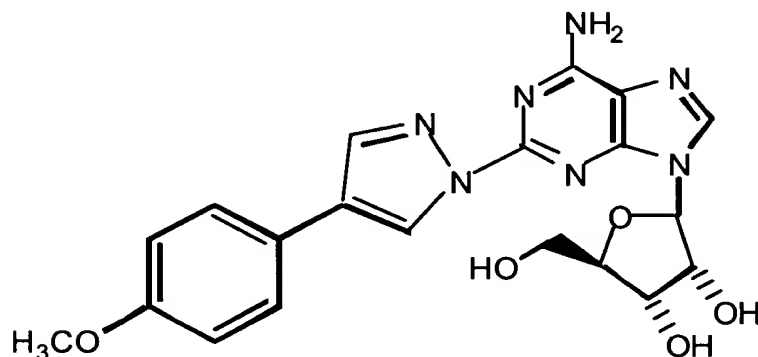
- (4S,2R,3R,5R)-2-{6-amino-2-[4-(4-chlorophenyl)pyrazolyl]purin-9-yl}-5-(hydroxymethyl)oxolane-3,4-diol (13)**
- 15

To a suspension of 2-hydrazinoadenosine (0.025 g, 0.08 mmol) in a 1:1 mixture of MeOH/AcOH was added 2-(4-chloro)malondialdehyde (0.022g, 0.12 mmol) and the mixture

was heated at 80 °C for 3 h. The precipitate formed was collected by filtration and washed with EtOH and Ether to afford 13. ¹HNMR (DMSO-d₆) δ3.5 (m, 1 H), 3.6 (m, 1 H), 3.8 (d, 1 H), 4.15 (d, 1 H), 4.2 (q, 2 H), 4.55 (m, 1H), 5.9 (d, 1H), 7.45 (d, 2 H), 7.75 (d, 2 H), 8.25 (s, 1H), 8.35 (s, 1 H), 8.9 (s, 1H).

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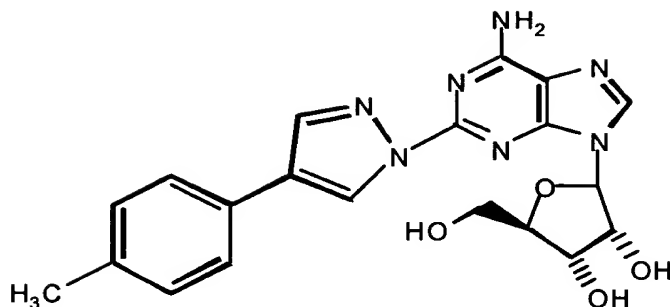
Example 3



10 **(4S,2R,3R,5R)-2-{6-amino-2-[4-(4-methoxyphenyl)pyrazolyl]purin-9-yl}-5-(hydroxymethyl)oxolane-3,4-diol (14)**

To a suspension of 2-hydrazinoadenosine (0.025 g, 0.08 mmol) in a 1:1 mixture of MeOH/AcOH was added 2-(4-methoxy)malondialdehyde (0.022g, 0.12 mmol) and the mixture was heated at 80 °C for 3 h. The precipitate formed was collected by filtration and washed with EtOH and Ether to afford 14. ¹HNMR (DMSO-d₆) δ3.55 (m, 1 H), 3.65 (m, 1 H), 3.75 (s, 3 H), 3.9 (d, 1 H), 4.15 (d, 1 H), 4.6 (m, 1 H), 5.9 (d, 1 H), 6.75 (d, 2 H), 7.6 (d, 2 H), 8.15 (s, 1H), 8.35 (s, 1 H), 8.8 (s, 1 H).

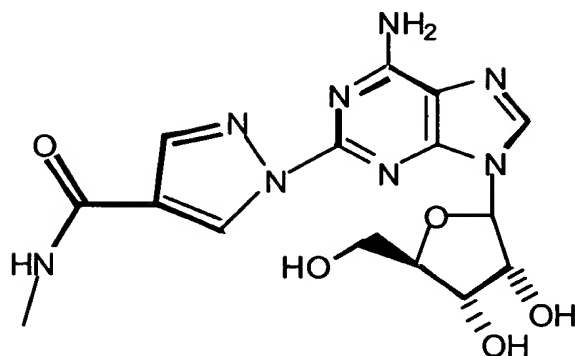
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Example 4

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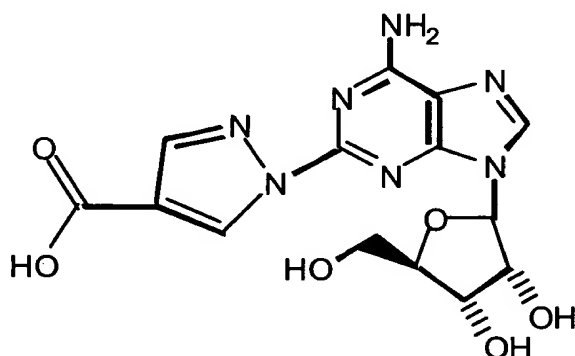
(4S,2R,3R,5R)-2-{{6-amino-2-[4-(4-methylphenyl)pyrazolyl]purin-9-yl}-5-(hydroxymethyl)oxolane-3,4-diol (15)}

To a suspension of 2-hydrazinoadenosine (0.025 g, 0.08 mmol) in a 1:1 mixture of
 10 MeOH/AcOH was added 2-(4-methyl)malondialdehyde (0.019g, 0.12 mmol) and the mixture
 was heated at 80 °C for 3 h. The precipitate formed was collected by filtration and washed
 with EtOH and Ether to afford **15**. ¹HNMR (DMSO-d₆) δ 3.55 (m, 1 H), 3.65 (m, 1 H), 3.75
 (s, 3 H), 3.9 (d, 1 H), 4.15 (d, 1 H), 4.6 (m, 1 H), 5.9 (d, 1 H), 6.75 (d, 2 H), 7.6 (d, 2 H),
 8.15 (s, 1 H), 8.35 (s, 1 H), 8.8 (s, 1 H).

Example 5

(1-{9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-aminopurin-2-yl}pyrazol-4-yl)-N-methylcarboxamide (16)

Compound (0.05 mg, 0.12 mmol) was added to 4 mL methylamine (40% sol. In water). The mixture heated at 65 °C in for 24 h. After concentration in vacuo, the residue was purified using prep. TLC (10% MeOH:DCM). ¹HNMR (CD₃OD) δ2.90 (s, 3 H), 3.78 (m, 1 H), 3.91 (m, 1 H), 4.13 (d, 1 H), 4.34 (d, 1 H), 4.64 (m, 1 H), 6.06 (d, 1 H), 8.11 (s, 1 H), 8.38 (s, 1 H), 9.05 (s, 1 H).

Example 6

1-{9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-aminopurin-2-yl}pyrazole-4-carboxylic acid (17)

Compound (0.05 mg, 0.12 mmol) was dissolved one equivalent of 1N NaOH. The solution was allowed to stir at Rt for 2h, then acidified to pH 4. The resulting precipitate was
 5 filtered and washed with water and ether. ¹HNMR (CD₃OD) Δ3.75 (m, 1 H), 3.90 (m, 1 H), 4.13 (d, 1 H), 4.43 (d, 1 H), 4.64 (m, 1H), 6.05 (d, 1H), 8.10 (s, 1H), 8.35 (s, 1 H), 9.05 (s, 1 H).

Example 7

10 Compositions of this invention were assayed to determine their affinity for the A2A receptor in a pig striatum membrane prep. Briefly, 0.2 mg of pig striatal membranes were treated with adenosine deaminase (2 U/ mL) and 50 mM Tris buffer (pH = 7.4) followed by mixing. To the pig membranes was added 2 μL of serially diluted DMSO stock solution of the compounds of this invention at concentrations ranging from 10 nM to 100 microM or the
 15 control received 2 microL of DMSO alone, then the trotted antagonist ZM 241385 in Tris buffer (50 mM, pH of 7.4) was added to achieve a final concentration of 2 nM . After incubation at 23 ° C for 2h, then the solutions were filtered using a membrane harvester using multiple washing of the membranes (3 x). The filter disks were counted in scintillation cocktail to determine the amount of displacement of tritiated ZM displaced by the
 20 compositions of this invention. Greater than a 5 point curve was used to generate Ki.'s. and the number of experiments is indicated in the column marked in Table 1 below.

Table 1

10290

Compound Number	A _{2a} Ki, nM	n
12	+++	2
13	++	3
14	++	1
15	++	3
16	++	2
17	-	1

+++ = 10-1,000 nM

++ = 1,000-10,000 nM

5 + = greater than 10,000 nM

- = greater than 100,000 nM